Examiner Interview

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Solid Oral Dosage Form Containing an Enhancer
U.S. Patent Application No. 09/510,560

merrion
pharmaceuticals

Pharmaceutical Development

- Drug must be in solution to be absorbed
- Products mature from liquids to solids
  - Elixirs were earliest dosage forms.
  - Pills were created by mixing liquids with excipients, forming wet masses which were allowed to dry
- First human dosage forms are almost always powder for reconstitution or solution
  - Using solutions is a more simplistic approach
  - Easier to formulate with small amounts of material
  - Avoids issue of getting drug to an absorbable state

Pharmaceutical Development

- Dosage Form Preference
  - Tablets are preferred over capsules
  - Powder filled capsules are preferred over liquid filled capsules
  - Liquid filled capsules are preferred over free flowing liquids

Pharmaceutical Development

- Advantages of solid forms
  - Solid state stability is better than solution state
  - Tabletting is the simplest and fastest pharmaceutical process
  - Tablets have the longest shelf life
  - Tamper evidence is greatest with tablets
  - Accuracy of dosing is greatest with solids
  - Shipping costs are lowest

Market Preference for Solid Forms

- Of the top 50 products in 2005:
  - 22 are available only as tablets
  - 2 are available only as capsules
  - 3 are available only as tablets and capsules
  - 27 products are available only as tablets or capsules
  - 12 are only available as injectables

Drug Enhancer Technology

- Drug delivery techniques also mature from liquids to solids
  - Transdermals
  - Intranasals/inhalations
  - Poorly permeable oral compounds

Drug Enhancer Technology

- Transdermals
  - Initial systems were liquids in pouches or gels (Key nitroglycerin (NTG), Ciba NTG, Ciba estradiol (E2); all introduced in the 80's)
  - Current marketed products are all soluble in the adhesive systems (NTG, E2, nicotine, fentanyl, clonidine, norethindrone, scopolamine, testosterone)
  - Liquid systems were developed for other products but never commercialized
  - Few drugs have sufficient solubility in medical grade adhesives
  - New technologies in development to allow other drugs to be delivered (microporation, iontophoresis)

Drug Enhancer Technology

- Intranasals/inhalations
  - No powder intranasals are marketed yet, though delivery devices are available
  - First insulin inhalation product dependent on development of powder technology

Drug Enhancer Technology

- Poorly permeable oral compounds
  - Digoxin absorption improved by a liquid filled capsule (1982)
  - Cyclosporine is a poorly permeable peptide
    - Was initially marketed in 1983 as an injectable and an oral liquid
    - Was marketed in 1990 as liquid-filled soft gel capsule
    - Was marketed in 1995 as a microemulsion based liquid and liquid filled capsule
    - Set a standard for emulsion-based systems

Drug Enhancer Technology

- Poorly permeable oral compounds (con't)
  - Merrion is an innovator in microemulsion liquid systems to deliver poorly permeable compounds:
    - US 5,633,226 (97), surfactants, lipids, fatty acid salt
    - US 5,444,041 (97), surfactants, lipids, fatty acid salt
    - US 5,646,109 (97), surfactants, lipids, fatty acid salt
    - US 5,688,761 (97), surfactants, lipids, other components may be present
    - US 5,707,648 (98), surfactants, lipids, PEG
    - No products have been commercialized using any of these technologies
    - The current technology was developed to overcome issues with these systems

Drug Enhancer Technology

- Poorly permeable oral compounds (con't.)
  - Starch capsules developed in part to meet need for shells compatible with surfactants
  - Sirolimus (rapamycin) was initially marketed as liquid dosage form and is now available as a tablet using nanocrystal technology
    - Patent 5,559121 (1996) discloses oral sirolimus compositions; only has liquid examples
    - Sirolimus patent 5,536,729 (1996) has oral liquid and starch capsule examples

Cited References

- Bachynsky et al. (U.S. Patent No. 5,190,748)
  - Compositions composed of emulsifiable systems of surfactants and lipids which are liquids or low melting point solids used to form liquids which are poured into capsules
  - Compositions do not require drug solutions, but use surfactants to facilitate solubility in systems that are liquid at the administration site

Cited References

- Fujii et al. (U.S. Patent No. 5,840,685)
  - Uses surfactant-based systems that are liquid at or below body temperature to deliver antibiotics vaginally
  - Discloses MCFA salts only in two-component enhancer systems in combination with other materials

Cited References

- Watts et al. (WO 97/05903)
  - Surfactants are used to form microemulsion-like systems that are liquid at or below body temperature.
  - All the examples use only starch capsules. The assignee bought the starch capsule technology from Warner-Lambert when they discontinued development. This technology has not been commercialized.
  - Most of the formulae disclosed in Watts are not compatible with commercially available capsules.
  - Additionally, they cannot be formed into tablets.